

Environmental Effects on Human Placental DNA Methylation and its Role in Development of Preeclampsia

Tisha Manase, TBIOMD 492, Mentor: Dr. Jutta Heller

Background & Introduction

- Preeclampsia: disorder in pregnant women characterized by hypertension following 20 weeks of pregnancy
- Preeclampsia is a major cause of maternal morbidity and mortality worldwide – contributes to ~16% of maternal deaths globally
- Preeclampsia currently has no definite cause, but research suggests a strong association to placental development and function
- Placenta is a highly complex organ responsible for providing the fetus with proper nutrients and oxygen, as well as performing waste removal and gas exchange
- Widely accepted theory for preeclampsia origin: inadequate placentation or poor development of placenta
- Abnormal development of placenta is directly linked to environmental risks and stressors:
 - Maternal obesity
 - Nutritional imbalance
 - Maternal stress
 - Lack of social support
- Environmental factors influence placental development through epigenetic mechanisms like DNA methylation
- DNA methylation regulates gene expression by silencing genes through addition of methyl groups onto DNA sequences
- Within placenta, genes are highly regulated – specifically hypomethylated (reduced methylation)
- DNA methylation has shown to be associated with development of preeclampsia

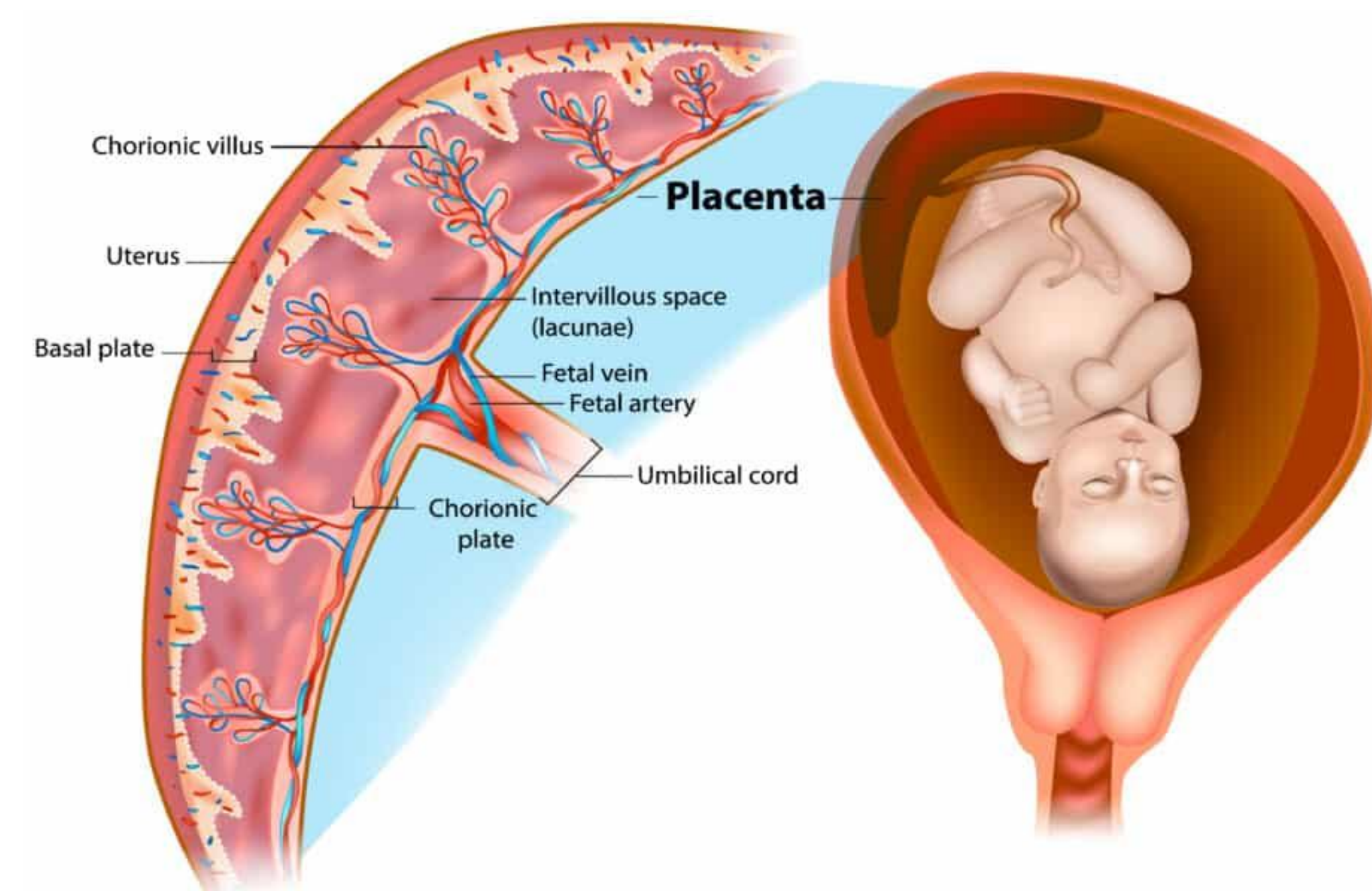


Figure 1. Diagram of placental anatomy and position in womb with fetus (<https://www.hypnobabies.com/your-amazing-placenta/>)

Methods

A literature review was synthesized to analyze multiple primary and secondary sources for determining how environmental influences may cause Preeclampsia through DNA methylation.

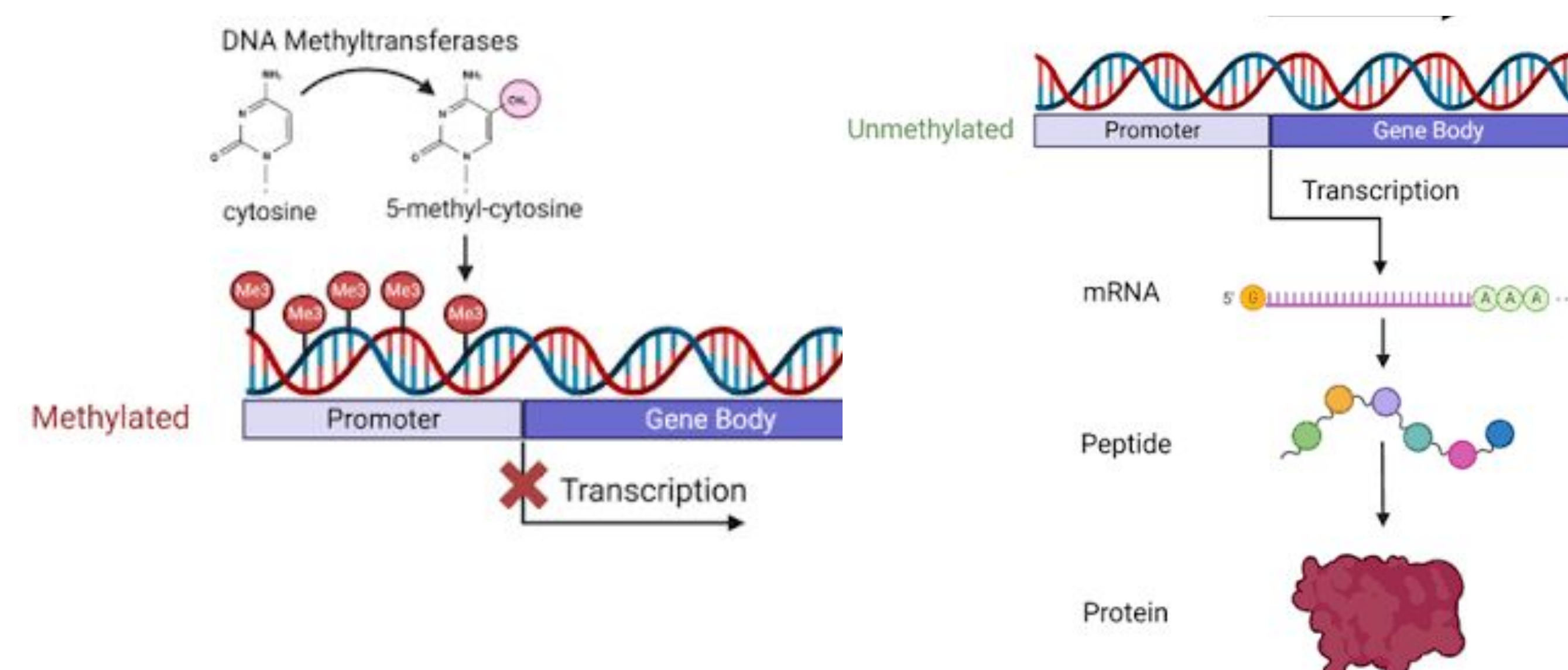


Figure 2. Diagram of DNA and downstream effects when methylated vs unmethylated (Figure from Wang et al., 2023)

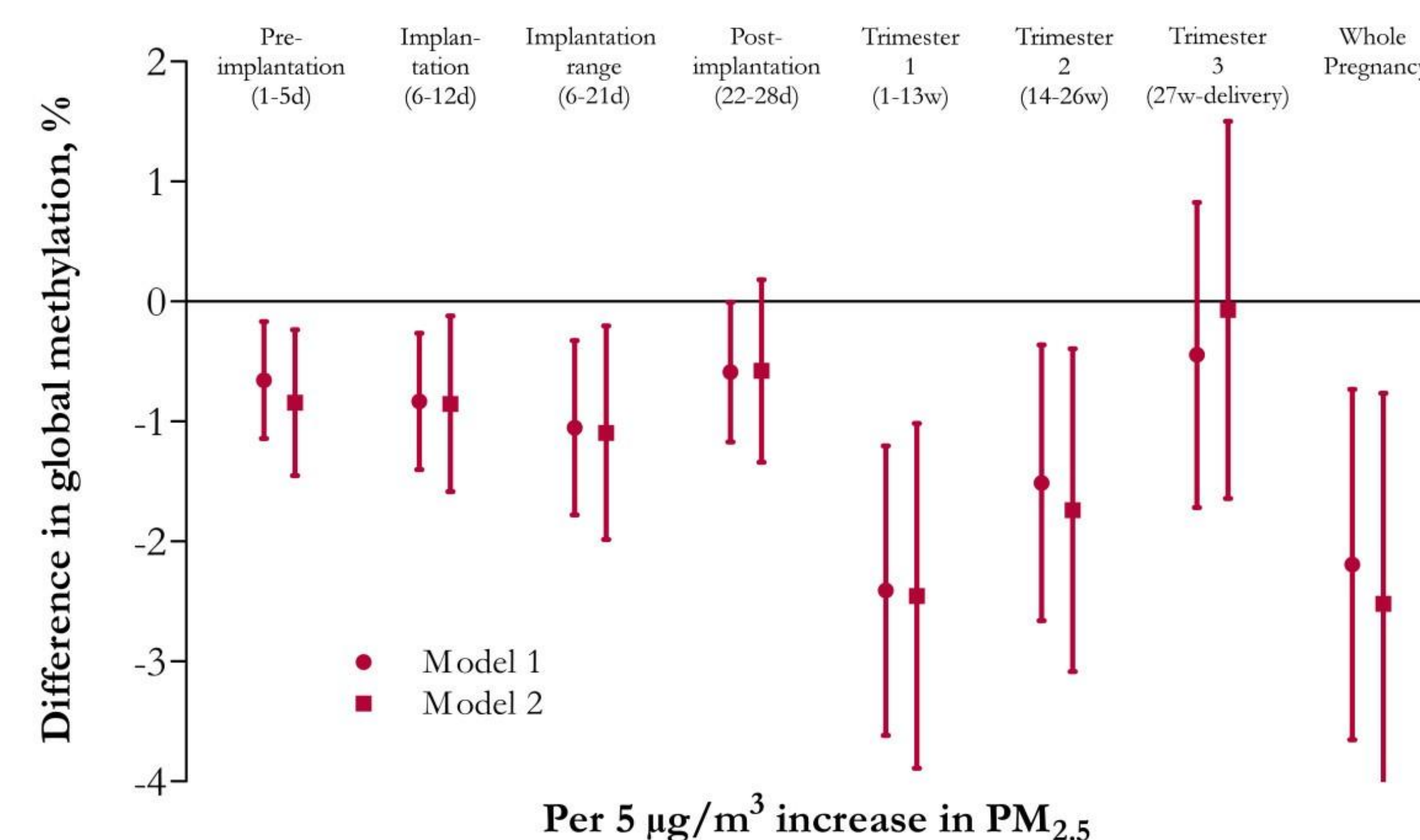


Figure 3. Relative difference (95% CI) in mean placental global DNA methylation for each 5 µg/m³ increase in fine particulate air pollution exposure during varying developmental windows. Model 1 is adjusted for demographic and clinical factors that may influence methylation while model 2 is adjusted for the same factors in addition to NO₂ and O₃ (Figure from Janssen et al., 2013)

Conclusion

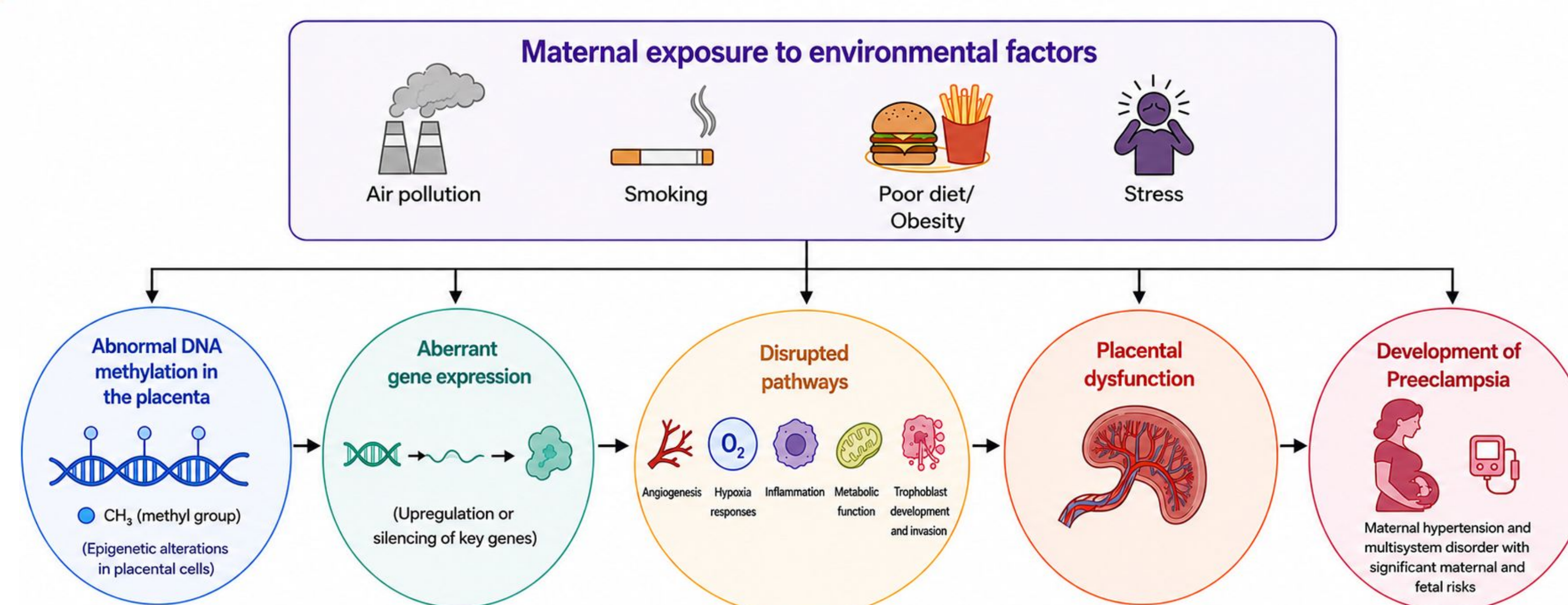


Image made by AI

Results / Findings

- **Environmental pollutants** are associated with differences in placental DNA methylation
 - One study: lower methylation levels in CpGs within **ADORA2B** gene
 - **ADORA2B** encodes protein receptor important for placental development
 - Activation of **ADORA2B** signaling has been demonstrated to contribute to development of preeclampsia
 - Another study: exposure to fine particles during pregnancy lowered global placental DNA methylation
- **Maternal obesity and nutritional imbalance** are major risks of preeclampsia
 - One study: higher methylation of **leptin gene** in placentas of obese mothers
 - Downregulation of leptin systems in placenta leads to loss of beneficial effects on placental development
 - Another study: pre-pregnancy obesity is linked to methylation changes in genes including **EGFL7**
 - **EGFL7**: signaling protein important for angiogenesis and vascular development – vital processes for proper placenta formation
- **Maternal stress and poor social support** are risk factors for preeclampsia
 - One study: prenatal social support is associated with methylation levels at CpGs – includes placental expression of **VGF** and **ILVBL**
 - Associated genes were enriched in biological pathways related to fetal growth, coagulation, energy metabolism, & neurodevelopment
 - Another study: mothers who experienced relief in a stress factor were likely to have higher methylation on **NR3C1** gene than control group
 - **NR3C1** encodes receptor that's involved in regulating stress
 - Stress is reduced → Risk of preeclampsia lowers

Future Research

- Continue to establish causal relationships between environmental influences, DNA methylation, and progression of preeclampsia
- Study the mechanisms and processes involved in placental DNA methylation to assess for new potential biomarkers
- Identify epigenetic signatures in placental tissue of preeclampsia
 - Then identify methylation-based biomarkers useful for early detection of preeclampsia
- Research diverse populations and address health disparities to see how these exposures interact with epigenetic mechanisms across different ethnicities, cultures, demographics, or populations

References

